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L3: Entry 31 of 41 File: USPT Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962477 A
TITLE: Screening methods for cytokine inhibitors

DEPR:
Another study with homogenized brain tissue correlated the expression of TNF mRNA with cognitive impairment and other related changes in HIV-infected patients (see, Glass, et al., Neurology 43:2230-2237 (1993)). Levels of mRNA were significantly greater in patients with HIV-associated dementia than in AIDS patients without dementia, or in seronegative controls. Pentoxifylline (PTX), a drug which blocks TNF release, was tested in HIV-positive patients alone and together with zidovudine (ZDV). The average HIV viral load was increased over baseline after treatment with PIX and ZDV, compared to higher levels in patients given either agent alone (see, Luke, et al., Int. J. Clin. Pharmacol. Ther. Toxicol. 31:343-350 (1993)). TNF levels were also correlated with the viral load in patients who had received both drugs.

DEPR:
Preferred compounds useful in the present invention include the loop diuretics and thiazides. Loop diuretics, e.g., furosemide, ethacrynic acid and bumetanide, are known to affect kidney function by blocking the re-absorption of sodium chloride (NaCl) in the medullary and cortical portions of the thick ascending limb of Henle's loop; thereby, reducing the osmotic gradient in the renal medulla and impairing the concentrating and diluting capacities of the kidney. Current clinical indications for the use of loop diuretics include hypertension, chronic congestive heart failure, acute pulmonary edema, nephrotic syndrome, chronic renal failure, chronic liver disease, brain edema and hyponatremic states. Thiazides (e.g., chlorthalidone, quinethazone, metolazone, indapamide, chlorothiazide, hydrochlorothiazide, bendroflumethiazide, cyclothiazide, hydroflumethiazide methychlothiazide, polythiazide, and trichloromethiazide) were among the first diuretic drugs discovered in the late 1950s. The mode of action and clinical indications of these drugs are substantially similar to the loop diuretics. See, Drug Evaluations (Subscription), Vol. II: "Renal-Urologic Drugs", American Medical Association (Winter 1993).

DEPR:
The net intracellular cAMP level can also be increased by inhibiting the cAMP degradation. To this end, several inhibitors of phosphodiesterases (PDEs), the enzyme that degrades cAMP to 5'-AMP will find use in the methods described herein. Examples of PDE inhibitors include type IV phosphodiesterase inhibitors (the isozyme family specific for cAMP), such as rolipram, RO 20-1724; methylxanthines such as pentoxifylline (a non-specific PDE inhibitor, see, e.g., European Patent Application No. 544,391 A1 to Eitan, et al.), theophylline, theobromine, and isomethylxanthine; pyrrolidinones and phenyl cycloalkane and cycloalkene derivatives, described in PCT publications Nos. WO 92/19594 and WO 92/10190). Surprisingly, RO 20-1724 showed inhibitory activity against TNF and was more effective than non-specific PDE inhibitors such as pentoxifylline.

DEPR:
For example, RA is a common systemic, autoimmune, inflammatory disorder expressed most commonly in the joints. As a highly variable disease, clinical manifestation ranges from a mild paucistricular form of brief duration to a relentless, progressive, destructive polyarthritis associated with systemic features. Frequently, RA is heralded by prodromal symptoms, such as fatigue, anorexia, weakness, and generally aching and stiffness that are not clearly

localized to the articular structure. Elevated levels of inflammatory and proinflammatory mediators have been found in the inflamed joints of patients with RA. On the other hand, IBD, including ulcerative colitis and Crohn's disease, which affects children and adolescent population, is largely associated with pain, distressing toilet habits, retardation of growth and suppression of pubertal development. Similar to RA, various inflammatory and proinflammatory mediators are found in the intestinal mucosa, and in the feces of patients with IBD. However, recent clinical results demonstrate a clear resolution of both severe RA and IBD upon administration of anti-TNF antibody. Another systemic condition, i.e., cachexia (wasting syndrome) has an adverse impact on the lives of many patients in the advanced stage of cancer and AIDS. Pentoxifylline and thalidomide have both been shown to be effective in reducing TNF activities in vitro and were both effective in vivo in improving cachexia conditions in cancer and AIDS patients respectively. Therefore, TNF has been found to be the key mediator in many systemic inflammatory conditions including RA, IBD, cachexia, infection, adult respiratory distress syndrome, asthma and others.

DEPR:
The abilities of several compounds to inhibit TNF, IL-1.alpha. and IL-1.beta. release in stimulated cells, including THP-1 cells, RAW cells and HEK cells were examined using methods described below. The results are summarized in Table I below for the inhibition of TNF. The compounds studied included verapamil, nicardipine, isradipine, RO 20-1724, loperamide, Rec 15/2375, diphenoxylate, amiloride, spironolactone, thalidomide, pentoxifylline, terbutaline and furosemide. A control (dexamethasone) was included.

DEPR:
A number of drugs tested at 10 .mu.M concentration achieved substantial inhibition of LPS (10 ng/ml)-stimulated TNF secretion by RAW264.7 cells, even comparable to that achieved by dexamethasone as indicated by the results of an initial screen. These include pentoxifylline (an inhibitor of cAMP phosphodiesterase; 57% inhibition), compound RO-20-1724 (47% inhibition; this is an average of three experiments), tamoxifen and nafoxidine (.about.65% inhibition by each), thioridazine and pimozide (anti-psychotic drugs; 60-70% inhibition), flunarizine (63% inhibition) and dithranol (an anti-psoriatic drug, and an inhibitor of leukotriene synthesis; 67% inhibition).

DEPR:
As the results in Table I demonstrate, surprisingly, most calcium channel blockers (i.e., (.+-.), (-) and (+)-verapamil, nicardipine, isradipine and Rec 15/2375 are effective in inhibiting the release of TNF in stimulated cells, and (+)-verapamil is much more effective than thalidomide or pentoxifylline.

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L3: Entry 33 of 41 File: USPT Jul 13, 1999

DOCUMENT-IDENTIFIER: US 5922595 A
TITLE: Cyclic GMP phosphodiesterase

BSPR:
Many inhibitors of PDEs have been identified and have undergone clinical evaluation. PDE3 inhibitors are being developed as antithrombotic agents, antihypertensive agents, and as cardiotonic agents useful in the treatment of congestive heart failure. Rolipram, a PDE4 inhibitor, has been used in the treatment of depression, and other inhibitors of PDE4 are undergoing evaluation as anti-inflammatory agents. Rolipram has also been shown to inhibit lipopolysaccharide (LPS) induced TNF-alpha which has been shown to enhance HIV-1 replication in vitro. Therefore, rolipram may inhibit HIV-1 replication (Angel, J. B. et al. (1995) AIDS 9:1137-44). Additionally, rolipram, based on its ability to suppress the production of cytokines such as TNF alpha and beta and interferon gamma, has been shown to be effective in the treatment of encephalomyelitis. Rolipram may also be effective in treating tardive dyskinesia and was effective in treating multiple sclerosis in an experimental animal model (Sommer, N. et al. (1995) Nat.Med. 1:244-248; Sasaki, H. et al. (1995) Eur. J. Pharmacol 282:71-76).

BSPR:
Theophylline is a nonspecific PDE inhibitor used in the treatment of bronchial asthma and other respiratory diseases. Theophylline is believed to act on airway smooth muscle function and in an anti-inflammatory or immunomodulatory capacity in the treatment of respiratory diseases (Banner, K. H. and Page, C. P. (1995) Eur. Respir. J. 8:996-1000). Pentoxifylline is another nonspecific PDE inhibitor used in the treatment of intermittent claudication and diabetes-induced peripheral vascular disease. Pentoxifylline is also known to block TNF-alpha production and may inhibit HIV-1 replication (Angel et al., supra).

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L3: Entry 29 of 41 File: USPT Mar 14, 2000

DOCUMENT-IDENTIFIER: US 6037346 A
TITLE: Local administration of phosphodiesterase inhibitors for the treatment of erectile dysfunction

BSPR:
Phosphodiesterases are a class of intracellular enzymes involved in the metabolism of the second messenger nucleotides, cyclic adenosine monophosphate (cAMP), and cyclic guanosine monophosphate (cGMP) (see, e.g., Doherty, "Oral, Transdermal, and Transurethral Therapies for Erectile Dysfunction" in Male Infertility and Dysfunction, Hellstrom, ed., Chapter 34 (New York, N.Y.: Springer-VerlagHellstrom, 1997)). Numerous phosphodiesterase inhibitors have previously been described in the literature for a variety of therapeutic uses, including treatment of obstructive lung disease, allergies, hypertension, angina, congestive heart failure and depression (see, e.g., Goodman and Gilman's The Pharmacological Basis of Therapeutic Ninth Edition, Chapter 34). Oral and parenteral administration of phosphodiesterase inhibitors, as alluded to above, have also been suggested for the treatment of erectile dysfunction (Doherty, supra; see also PCT Publication Nos. WO 96/16644, and WO 94/28902). The phosphodiesterases have been classified into seven major families, Types I-VII, based on amino acid or DNA sequences. The members of the family vary in their tissue, cellular and subcellular distribution, as well as their links to cAMP and cGMP pathways. For example, the corpora cavernosa contains: type III phosphodiesterases, which are cAMP-specific cGMP inhibitable; type IV phosphodiesterases, the high affinity, high-specificity cAMP-specific form; and type V phosphodiesterases, one of the cGMP-specific forms.

BSPR:
Various compounds are known as inhibitors of phosphodiesterases are known, including vinpocetine, milrinone, amrinone, pimobendan, cilostamide, enoximone, peroximone, vesnarinone, rolipram, RO20-1724, zaprinast, dipyridamole, pentoxifylline, sildenafil citrate (Viagra.RTM.), doxazosin, papaverine, prazosin, terazosin, trimazosin, and hydralazine. PCT Publication No. WO 94/28902 discloses a series of pyrazole [4,3-d]pyrimidin-7-ones cGMP phosphodiesterase inhibitors. PCT Publication No. WO 96/16644 also discloses a variety of cGMP phosphodiesterase inhibitors, including griseolic acid derivatives, 2-phenylpurinone derivatives, phenylpyridone derivatives, fused and condensed pyrimidines, a pyrimdopyrimidine derivative, a purine compound, a quinazoline compound, a phenylpyrimidone derivative, an imidazoquinoxalinone derivative or aza analogues thereof, a phenylpyridone derivative, and others.

DEPR:
Other phosphodiesterase inhibitors that may be used in the method of this invention include nonspecific phosphodiesterase inhibitors such as theophylline, IBMX, pentoxifylline and papaverine, and direct vasodilators such as hydralazine.

[General]

Heart failure (congestive heart failure): Symptomatic myocardial dysfunction resulting in a characteristic pattern of hemodynamic, renal, and neurohormonal responses.

(For heart failure in children, see Ch. 261.)

The Merck Manual of Diagnosis and Therapy
Section 16. Cardiovascular Disorders
Chapter 203. Heart Failure

Topics

No definition of heart failure (HF) is entirely satisfactory. Congestive heart failure (CHF) develops when plasma volume increases and fluid accumulates in the lungs, abdominal organs (especially the liver), and peripheral tissues.

Physiology

At rest and during exercise, cardiac output (CO), venous return, and distribution of blood flow with O_2 delivery to the tissues are balanced by neurohumoral and intrinsic cardiac factors. Preload, the contractile state, afterload, the rate of contraction, substrate availability, and the extent of myocardial damage determine left ventricular (LV) performance and myocardial O_2 requirements. The Frank-Starling principle, cardiac reserve, and the oxyhemoglobin dissociation curve play a role.

Preload (the degree of end-diastolic fiber stretch) reflects the end-diastolic volume, which is influenced by diastolic pressure and the composition of the myocardial wall. For clinical purposes, the end-diastolic pressure, especially if above normal, is a reasonable measure of preload in many conditions. LV dilatation, hypertrophy, and changes in myocardial distensibility or compliance modify preload.

The **contractile state** in isolated cardiac muscle is characterized by the force and velocity of contraction, which are difficult to measure in the intact heart. Clinically, the contractile state is often expressed as the ejection fraction (LV stroke volume/end-diastolic volume).

Afterload (the force resisting myocardial fiber shortening after stimulation from the relaxed state) is determined by the chamber pressure, volume, and wall thickness at the time of aortic valve opening. Clinically, afterload approximates systemic BP at or shortly after aortic valve opening and represents peak systolic wall stress. The **heart rate and rhythm** also influence cardiac performance.

Reduced substrate availability (eg, of fatty acid or glucose), particularly if O_2 availability is reduced, can impair the vigor of cardiac contraction and myocardial performance.

Tissue damage (acute with MI or chronic with fibrosis due to various diseases) impairs local myocardial performance and imposes an additional burden on viable myocardium.

The **Frank-Starling principle** states that the degree of end-diastolic fiber stretch (preload) within a physiologic range is proportional to the systolic performance of the ensuing ventricular contraction (Fig. 203-1). This mechanism operates in HF, but, because ventricular function is abnormal, the response is inadequate. If the Frank-Starling curve is depressed, fluid retention, vasoconstriction, and a cascade of neurohumoral responses lead to the syndrome of CHF. Over time, LV remodeling (change from the normal ovoid shape) with dilatation and hypertrophy further compromises cardiac performance, especially during physical stress. Dilatation and hypertrophy may be accompanied by increased diastolic stiffness.

Cardiac reserve (unused ability of the resting heart to deliver O_2 to the tissues) is an important component of cardiac function during emotional or physical stress. Its mechanisms include increases in heart rate, systolic and diastolic volume, stroke volume, and tissue extraction of O_2. For example, in well-trained young adults during maximal exercise, heart rate may increase from 55 to 70 at rest to 180 beats/min; CO (stroke volume × heart rate) may increase from its normal resting value of 6 to >= 25 L/min; and O_2 consumption can increase from 250 to >= 1500 mL/min. In the normal young adult at rest, arterial blood contains about 18 mL O_2/dL of blood, and mixed venous or pulmonary artery blood contains about 14 mL/dL. The arteriovenous O_2 difference (A-VO_2) is thus about 4.0 ± 0.4 mL/dL. Even maximal CO during exercise is insufficient to meet tissue metabolic needs; hence, the tissues extract more O_2, and mixed venous blood O_2 content falls considerably. A-VO_2 may increase to about 12 to 14 mL/dL. Increased A-VO_2 due to lower venous O_2 content is a common adaptive mechanism in HF.

The **oxyhemoglobin dissociation curve** (see Fig. 203-2) influences O_2 availability to the tissues and can provide another reserve mechanism in HF. The position of this curve is frequently expressed as P_{50} (the partial pressure of O_2 in blood at 50% oxyhemoglobin saturation). An increase in the normal P_{50} (27 ± 2 mm Hg) indicates a rightward shift of the oxyhemoglobin dissociation curve (decreased affinity of Hb for O_2). For a given PO_2, less O_2 is combined with Hb, and the saturation is lower; thus, at the capillary level, more O_2 is released and available to the tissues. Increased hydrogen ion concentration (reduced pH) shifts the curve to the right (Bohr effect), as does increased concentration of 2,3-diphosphoglycerate in RBCs, which alters the spatial relationships within the Hb molecule.

Classification and Etiology

In many forms of heart disease, the clinical manifestations of HF may reflect impairment of the left or right ventricle.

Left ventricular (LV) failure characteristically develops in coronary artery disease, hypertension, and most forms of cardiomyopathy and with congenital defects (eg, ventricular septal defect, patent ductus arteriosus with large shunts).

Right ventricular (RV) failure is most commonly caused by prior LV failure (which increases pulmonary venous pressure and leads to pulmonary arterial hypertension) and tricuspid regurgitation. Mitral stenosis, primary pulmonary hypertension, multiple pulmonary emboli, pulmonary artery or valve stenosis, and RV infarction are also causes. Volume overload and increased systemic venous pressure may also occur in polycythemia or overtransfusion, acute renal failure with overhydration, and obstruction of either vena cava simulating HF. In these conditions, myocardial function may be normal.

HF is manifest by **systolic or diastolic dysfunction,** or both. Combined systolic and diastolic abnormalities are common.

In systolic dysfunction (primarily a problem of ventricular contractile dysfunction), the heart fails to provide tissues with adequate circulatory output. A wide variety of defects in energy utilization, energy supply, electrophysiologic functions, and contractile element interaction occur, which appear to reflect abnormalities in intracellular Ca^{++} modulation and cyclic adenosine monophosphate (cAMP) production. Systolic dysfunction has numerous causes; the most common are coronary artery disease, hypertension, and dilated congestive cardiomyopathy. There are many known and probably many unidentified causes for dilated myocardiopathy. More than 20 viruses have been identified as causal. Toxic substances damaging the heart include alcohol, a variety of organic solvents, certain chemotherapeutic drugs (eg, doxorubicin), β-blockers, Ca blockers, and antiarrhythmic drugs.

Diastolic dysfunction (resistance to ventricular filling not readily measurable at the bedside) accounts for 20 to 40% of cases of HF. It is generally associated with prolonged ventricular relaxation time, as measured during isovolumic relaxation (the time between aortic valve closure and mitral valve opening when ventricular pressure falls rapidly). Resistance to filling (ventricular stiffness) directly relates to ventricular diastolic pressure; this resistance increases with age, probably reflecting myocyte loss and increased interstitial collagen deposition. Diastolic dysfunction is presumed to be dominant in hypertrophic cardiomyopathy, circumstances with marked ventricular hypertrophy (eg, hypertension, advanced aortic stenosis), and amyloid infiltration of the myocardium.

High output failure is HF associated with a persistent high CO that eventually results in ventricular dysfunction. Conditions associated with high CO include anemia, beriberi, thyrotoxicosis, pregnancy, advanced Paget's disease, and arteriovenous fistula. CHF may develop in high-output states but is often reversible by treating the underlying cause. CO is elevated in various forms of cirrhosis, but the onset of congestion reflects cardiac and hepatic mechanisms of fluid retention.

Pathophysiology

In LV failure, CO declines and pulmonary venous pressure increases. Elevated pulmonary capillary pressure to levels that exceed the oncotic pressure of the plasma proteins (about 24 mm Hg) leads to increased lung water, reduced pulmonary compliance, and a rise in the O_2 cost of the work of breathing. Pulmonary venous hypertension and edema resulting from LV failure significantly alter pulmonary mechanics and, thereby, ventilation/perfusion relationships. Dyspnea correlates with elevated pulmonary venous pressure and the resultant increased work of breathing, although the precise cause is debatable. When pulmonary venous hydrostatic pressure exceeds plasma protein oncotic pressure, fluid

extravasates into the capillaries, the interstitial space, and the alveoli. Pleural effusions characteristically accumulate in the right hemithorax and later bilaterally. Lymphatic drainage is greatly enhanced but cannot overcome the increase in lung water. Unoxygenated pulmonary arterial blood is shunted past nonaerated alveoli, decreasing mixed pulmonary capillary PO_2. A combination of alveolar hyperventilation due to increased lung stiffness and reduced PA_{O2} is characteristic of LV failure. Thus, arterial blood gas analysis reveals an increased pH and a reduced Pa_{O2} (respiratory alkalosis) with decreased saturation reflecting increased intrapulmonary shunting. Typically, Pa_{CO2} is reduced also. A Pa_{CO2} above normal signifies alveolar hypoventilation possibly due to respiratory muscle failure and requires urgent ventilatory support.

In RV failure, systemic venous congestive symptoms develop. Moderate hepatic dysfunction commonly occurs in CHF secondary to RV failure, with usually modest increases in conjugated and unconjugated bilirubin, prothrombin time, and hepatic enzymes (eg, alkaline phosphatase, AST, ALT). However, in severely compromised circulatory states with markedly reduced splanchnic blood flow and hypotension, increases due to central necrosis around the hepatic veins may be severe enough to suggest hepatitis with acute liver failure. Reduced aldosterone breakdown by the impaired liver further contributes to fluid retention.

In systolic dysfunction, inadequate ventricular emptying leads to increased preload, diastolic volume, and pressure. Sudden (as in MI) and progressive (as in dilated cardiomyopathy) myocyte loss induces ventricular remodeling, resulting in increased wall stress accompanied by apoptosis (accelerated myocardial cell death) and inappropriate ventricular hypertrophy. Later, the ejection fraction falls, resulting in progressive pump failure. Systolic HF may primarily affect the LV or the RV (see above), although failure of one ventricle tends to lead to failure of the other.

In diastolic dysfunction, increased resistance to LV filling as a consequence of reduced ventricular compliance (increased stiffness) results in prolonged ventricular relaxation (an active state following contraction) and alters the pattern of ventricular filling. Ejection fraction may be normal or increased. Normally, about 80% of the stroke volume enters the ventricle passively in early diastole, reflected in a large e wave and smaller a wave on pulsed-wave Doppler echocardiography. Generally, in diastolic LV dysfunction the pattern is reversed, accompanied by increased ventricular filling pressure and a-wave amplitude.

Whether the failure is primarily systolic or diastolic and regardless of which ventricle is affected, various hemodynamic, renal, and neurohumoral responses may occur.

Hemodynamic responses: With reduced CO, tissue O_2 delivery is maintained by increasing A-VO_2. Measurement of A-VO_2 with systemic arterial and pulmonary artery blood samples is a sensitive index of cardiac performance and reflects, via the Fick equation ($VO_2 = CO \times A\text{-}VO_2$), CO (inversely related) and the body's O_2 consumption (VO_2--directly related).

Increased heart rate and myocardial contractility, arteriolar constriction in selected vascular beds, venoconstriction, and Na and water retention compensate in the early stages for

reduced ventricular performance. Adverse effects of these compensatory efforts include increased cardiac work, reduced coronary perfusion, increased cardiac preload and afterload, fluid retention resulting in congestion, myocyte loss, increased K excretion, and cardiac arrhythmia.

Renal responses: The mechanism by which an asymptomatic patient with cardiac dysfunction develops overt CHF is unknown, but it begins with renal retention of Na and water, secondary to decreased renal perfusion. Thus, as cardiac function deteriorates, renal blood flow decreases in proportion to the reduced CO, the GFR falls, and blood flow within the kidney is redistributed. The filtration fraction and filtered Na decrease, but tubular resorption increases.

Neurohumoral responses: Increased activity of the renin-angiotensin-aldosterone system influences renal and peripheral vascular response in HF. The intense sympathetic activation accompanying HF stimulates the release of renin from the juxtaglomerular apparatus near the descending loop of Henle in the kidney. Probably, decreased arterial systolic stretch secondary to declining ventricular function also stimulates renin secretion. Reflex and adrenergic stimulation of the renin-angiotensin-aldosterone system produces a cascade of potentially deleterious effects: Increased aldosterone levels enhance Na reabsorption in the distal nephron, contributing to fluid retention. Renin produced by the kidney interacts with angiotensinogen, producing angiotensin I from which is cleaved the octapeptide angiotensin II by ACE. Angiotensin II has various effects believed to enhance the syndrome of CHF, including stimulation of the release of arginine vasopressin (AVP), which is antidiuretic hormone (ADH); vasoconstriction; enhanced aldosterone output; efferent renal vasoconstriction; renal Na retention; and increased norepinephrine release. Angiotensin II is also believed to be involved in vascular and myocardial hypertrophy, thus contributing to the remodeling of the heart and peripheral vasculature, which contributes to HF in various myocardial and other heart diseases.

Plasma norepinephrine levels are markedly increased, largely reflecting intense sympathetic nerve stimulation, because plasma epinephrine levels are not increased. High plasma norepinephrine levels in patients with CHF are associated with a poor prognosis.

The heart contains many neurohormonal receptors (α_1, β_1, β_2, β_3, adrenergic, muscarinic, endothelin, serotonin, adenosine, angiotensin II). In patients with HF, β_1 receptors (which constitute 70% of cardiac β receptors), but not the other adrenergic receptors, are down-regulated, potentially adversely affecting myocardial function. This down-regulation, which is probably a response to intense sympathetic overdrive, has been detected even in asymptomatic patients with the early stages of HF. Altered myocardial stimulator or receptor functions for various other neurohormonal factors may adversely influence myocyte performance in HF.

Serum levels of atrial natriuretic peptide (released in response to increased atrial volume and pressure load) and brain natriuretic peptide (released from the ventricle in response to ventricular stretch) are markedly increased in patients with CHF. These peptides enhance renal excretion of Na, but, in patients with CHF, the effect is blunted by decreased renal perfusion pressure, receptor down-regulation, and perhaps enhanced enzymatic degradation. Serum atrial natriuretic peptide appears to be important for diagnosis and prognosis in CHF and correlates well with functional impairment.

AVP is released in response to a fall in BP or ECF volume and by the effects of various neurohormonal stimuli. An increase in plasma AVP diminishes excretion of free water by the kidney and may contribute to the hyponatremia of HF. AVP levels in CHF vary, but experimental AVP blockers have increased water excretion and serum Na levels.

Other sequelae: Protein-losing enteropathy characterized by marked hypoalbuminemia, ischemic bowel infarction, acute and chronic GI hemorrhage, and malabsorption may result from severe chronic venous hypertension. Peripheral gangrene in the absence of large vessel occlusion or chronic irritability and decreased mental performance may result from chronic markedly reduced PO_2, reflecting severely reduced cerebral blood flow and hypoxemia.

Cardiac cachexia (loss of lean tissue >= 10%) may accompany severely symptomatic HF. The failing heart produces tumor necrosis factor-α, which is a key cytokine in the development of catabolism and possibly of cardiac cachexia. Marked anorexia is characteristic of the syndrome. Restoring cardiac function to normal can reverse cardiac cachexia.

Symptoms and Signs

HF may be predominantly right-sided or left-sided and may develop gradually or suddenly (as with acute pulmonary edema).

Cyanosis may occur with any form of HF. The cause may be central and may reflect hypoxemia. A peripheral component due to capillary stasis with increased A-VO_2 and resultant marked venous oxyhemoglobin unsaturation may also be present. Improved color of the nail bed with vigorous massage suggests peripheral cyanosis. Central cyanosis cannot be altered by increasing local blood flow.

LV failure: Pulmonary venous hypertension may become apparent with tachycardia, fatigue on exertion, dyspnea on mild exercise, and intolerance to cold. Paroxysmal nocturnal dyspnea and nocturnal cough reflect the redistribution of excess fluid into the lung with the recumbent position. Occasionally, pulmonary venous hypertension and increased pulmonary fluid manifest as bronchospasm and wheezing. Cough may be prominent, and pink-tinged or brownish sputum due to blood and the presence of HF cells is common. Frank hemoptysis due to ruptured pulmonary varices with massive blood loss is uncommon but may occur. Signs of chronic LV failure include diffuse and laterally displaced apical impulse, palpable and audible ventricular (S_3) and atrial gallops (S_4), accentuated pulmonic second sound, and inspiratory basilar rales. Right-sided pleural effusion is common.

Acute pulmonary edema is a life-threatening manifestation of acute LV failure secondary to sudden onset of pulmonary venous hypertension. A sudden rise in LV filling pressure results in rapid movement of plasma fluid through pulmonary capillaries into the interstitial spaces and alveoli. The patient presents with extreme dyspnea, deep cyanosis, tachypnea, hyperpnea, restlessness, and anxiety with a sense of suffocation. Pallor and diaphoresis are common. The pulse may be thready, and BP may be difficult to obtain. Respirations are labored, and rales are widely dispersed over both lung fields anteriorly and posteriorly. Some patients manifest marked bronchospasm or wheezing (cardiac asthma). Noisy

respiratory efforts often render cardiac auscultation difficult, but a summation gallop, merger of S_3 and S_4, may be heard. Hypoxemia is severe. CO_2 retention is a late, ominous manifestation of secondary hypoventilation and requires immediate attention.

RV failure: The principal symptoms include fatigue; awareness of fullness in the neck; fullness in the abdomen, with occasional tenderness in the right upper quadrant (over the liver); ankle swelling; and, in advanced stages, abdominal swelling due to ascites. Edema over the sacrum is likely in supine patients. Signs include evidence of systemic venous hypertension, abnormally large a or v waves in the external jugular pulse, an enlarged and tender liver, a murmur of tricuspid regurgitation along the left sternal border, RV S_3 and S_4, and pitting edema of the lowest parts of the body.

Diagnosis

Although symptoms and signs (eg, exertional dyspnea, orthopnea, edema, tachycardia, pulmonary rales, a third heart sound, jugular venous distention) have a diagnostic specificity of 70 to 90%, the sensitivity and predictive accuracy are low.

Recommended laboratory tests include CBC, blood creatinine, BUN, electrolytes (eg, Mg, Ca), glucose, albumin, and liver function tests. Thyroid function test results should be assessed in patients with atrial fibrillation and in selected, especially older, persons. In patients with suspected coronary artery disease, stress testing with radionuclide or ultrasound imaging or coronary angiography may be indicated. Endocardial biopsy is of limited usefulness.

ECG should be performed in all patients with HF, although findings are not specific; ambulatory ECG is not generally useful. Various abnormalities (eg, of ventricular hypertrophy, MI, or bundle branch block) may provide etiologic clues. Recent onset of rapid atrial fibrillation may precipitate acute LV or RV failure. Frequent premature ventricular contractions may be secondary and may subside when the HF is treated.

Chest x-ray should be performed in all patients. Pulmonary venous congestion and interstitial or alveolar edema are characteristics of pulmonary edema. Kerley B lines reflect chronic elevation of left atrial pressure and chronic thickening of the intralobular septa from edema. Microvascular volume increases, most strikingly in dependent areas, ie, the bases in upright posture. Careful examination of the cardiac silhouette, evaluation of chamber enlargement, and a search for cardiac calcifications may reveal important etiologic clues.

Echocardiography can help evaluate chamber dimensions, valve function, ejection fraction, wall motion abnormalities, and LV hypertrophy. Doppler or color Doppler echocardiography accurately detects pericardial effusion, intracardiac thrombi, and tumors and recognizes calcifications within the cardiac valves, mitral annulus, and the wall of the aorta. Underlying coronary artery disease is strongly suggested by localized or segmental wall motion abnormalities. Doppler studies of mitral and pulmonary venous inflow are often useful in identifying and quantitating LV diastolic dysfunction.

Treatment

Even in the most urgent situation, the cause of HF must be determined. Correctable

conditions require immediate treatment, which usually begins before the etiologic evaluation is completed. For patients requiring hospitalization, initial nonspecific treatment includes bed rest with the head elevated or chair rest with the feet dependent, nasal O_2 (often at 3 L/min for 24 to 36 hr), and sedation as needed.

Drug treatment of systolic dysfunction: Drug treatment of systolic dysfunction primarily involves diuretics, ACE inhibitors, digitalis, and β-blockers; most patients are treated with at least two of these classes.

Diuretics (see Table 203-1) may improve ventricular function even in asymptomatic patients. Loop diuretics are preferred; the most commonly used is IV or po furosemide. IV doses (usually 20 to 40 mg, increased to 320 mg if needed) are often used initially because of quick onset and peak action in about 30 minutes. In resistant cases, chlorothiazide 250 mg IV; bumetanide 0.5 to 2 mg po, 0.5 to 1.0 mg IV; or metolazone po (dosage varies with formulation) may have an additive effect. Overdosage of loop diuretics may cause hypovolemia, hyponatremia, hypomagnesemia and profound hypokalemia, so close electrolyte monitoring is essential. Diuretics may also induce renal failure and enhance the intense sympathetic stimulation characteristic of HF. K-sparing drugs may be used to offset the K-losing effects of loop diuretics, but hyperkalemia may complicate their use. Nonetheless, adding spironolactone to ACE inhibitor or other therapy may improve cardiac function and prognosis. Thiazide diuretics are not usually effective in patients with advanced symptoms of CHF.

The clinical efficacy of diuretics depends on dietary Na restriction using a stepped approach: eliminating salt at the table and avoiding heavily salted foods; eliminating salt from cooking and consuming about 1.2 to 1.8 g/day of Na^+; and, in the most severely ill, consuming < 1 g/day of Na through restriction to low-Na foods. A log of daily weight should be maintained by the patient to enhance ambulatory care of HF and to help prevent recurrent hospitalizations by detecting early evidence of Na^+ and water accumulation.

ACE inhibitors cause peripheral arterial and venous vasodilatation, sustained decreases in LV filling pressure at rest and on exercise due to venodilation, decreased systemic vascular resistance, favorable effects on remodeling, possible improved diastolic function, probable reduced loss of myocardial cells, and a negative inotropic effect on the failing heart. Various ACE inhibitors enhance survival in HF and reduce the incidence of recurrent angina and MI in coronary artery disease. Volume expansion and renal failure reduce their usual benefit. Side effects include a decrease in BP (sometimes severe) in almost all patients, especially those with hyponatremia. Moderate renal insufficiency may result from vasodilation of the efferent glomerular arteriole. K retention may occur due to reduced aldosterone effect, especially in patients receiving K supplements. Cough occurs in 5 to 20% of patients, probably due to accumulation of bradykinin as a result of reduced breakdown to inactive metabolites. Occasionally, rash or dysgeusia occurs. Angioneurotic edema is rare but can be life threatening.

ACE inhibitors are started in small doses, which are gradually increased, then continued indefinitely; doses should be adjusted upward as tolerated. Usual doses are captopril 25 to 50 mg/day, enalapril and lisinopril 2.5 to 5 mg/day, and quinapril 10 mg/day. Although an early effect may be observed, the full drug effect is usually not seen for 2 to 4 wk or considerably longer. Large doses produce a similar frequency of side effects as lower doses but are more effective (studies showing survival and other benefits have generally used

large doses).

The dose of a coadministered diuretic may frequently be reduced, especially if ACE inhibitor-induced renal insufficiency occurs. Aspirin may reduce the effect of ACE inhibitors in HF, possibly because it inhibits the effects of kinins.

The **angiotensin II receptor blocker** losartan 25 to 50 mg/day has effects similar to those of ACE inhibitors, although comparative trials have not been reported. Theoretically, cough should not occur because losartan does not influence kinins.

Digitalis preparations have many actions, including weak inotropism; blockade of the atrioventricular node, thus slowing the ventricular rate in atrial fibrillation or prolonging PR time in sinus rhythm; weak vasoconstriction; and improved renal blood flow. The drug is widely prescribed in the USA, although its role continues to be debated and its usefulness in HF in the absence of atrial fibrillation is controversial.

Digoxin is the most commonly prescribed digitalis preparation. It is excreted by the kidney with an elimination half-life of 36 to 48 h in patients with normal renal function. Patients with reduced renal function require lower doses. Oral bioavailability of digoxin tablets is around 65 to 75%. Digitoxin, an alternative in patients with known or suspected renal disease, is largely excreted in the bile and is thus not influenced by abnormal renal function.

Digoxin modestly improves LV function, allows reduced diuretic dosage, and reduces the need for hospitalization. Unlike ACE inhibitors, digoxin does not improve exercise tolerance. When digoxin is withdrawn in HF, the hospitalization rate and symptoms increase, although digoxin does not appear to influence mortality. Thus, digoxin is useful in symptomatic HF when used with diuretics and an ACE inhibitor. Digoxin is most effective in patients with large LV end-diastolic volumes and a third heart sound.

Digoxin (0.25 to 0.50 mg/day depending on body size) in patients with normal renal function will achieve full digitalization in about 1 wk (5 half-lives). Digoxin 1 mg IV administered as 0.5 mg initially, then 0.25 mg at 8 and 16 h (or 1.25 mg po administered as 0.5 mg initially, then 0.25 mg at 8, 16, and 24 h), should achieve adequate levels in tissue and plasma in the absence of toxicity. These doses are followed by 0.125 to 0.375 mg/day depending on body size; the elderly rarely need > 0.125 mg/day. Patients with reduced renal function require lower doses.

Digoxin (and all digitalis glycosides) has a narrow therapeutic-toxic threshold. About 80% of the therapeutic effect can be achieved with serum levels of 1.0 to 1.5 ng/mL, generally well below the toxic threshold of >= 2 ng/mL. In the management of atrial fibrillation, moderately low doses of digoxin may be combined with β-blockers or Ca blockers (eg, verapamil, diltiazem), which have a significant atrioventricular blocking effect, to control ventricular rate at rest or during exercise.

Digoxin prolongs conduction in the atrioventricular node. First-degree heart block is common and, if not progressive, digoxin dosage need not be adjusted. Wenckebach phenomenon may occur. The most important toxic effects of digitalis are life-threatening arrhythmias due to complete heart block or ventricular arrhythmia. Digitalis increases the automaticity of Purkinje's fibers and may enhance reentry, resulting in coupled extrasystoles, ventricular fibrillation, or ventricular tachycardia. Bidirectional ventricular

tachycardia is pathognomonic of digitalis toxicity. Nonparoxysmal junctional tachycardia in the presence of atrial fibrillation is a serious sign of digitalis toxicity but is frequently overlooked.

Hypokalemia and hypomagnesemia (often caused by diuretics) potentiate the capacity of digoxin to induce malignant ventricular arrhythmia or heart block. Recognition and treatment of electrolyte depletion are mandatory in patients taking diuretics and digoxin, except in the presence of atrioventricular block, in which a temporary pacemaker must be functioning prior to correcting the electrolyte abnormality.

Other manifestations of digitalis toxicity include nausea, vomiting, anorexia, diarrhea, confusion, amblyopia, and rarely xerophthalmia.

The first step in treating digitalis toxicity is to discontinue the drug. The ECG should be closely monitored, and if serum K is low, 80 mEq of potassium chloride IV should be given in 1 L 5% D/W at 6 mL/min (0.5 mEq/min). Low serum Mg is treated with magnesium sulfate 1 g q 6 h for four doses IM or IV if mild or 5 g/h in 5% D/W over 3 h (28 mg/min). Administration of digoxin immune Fab (if available) is better than administration of another antiarrhythmic drug. Ventricular arrhythmias are treated with lidocaine or phenytoin. Heart block with slow ventricular rate is best treated with a temporary perivenous pacemaker. Isoproterenol is contraindicated because of the increased tendency to ventricular arrhythmia.

Several **inotropic drugs** have been evaluated in the treatment of HF, but, except for digoxin, preparations have shown increased mortality.

With careful administration of **β-blockers,** some patients, especially those with idiopathic dilated cardiomyopathy, will improve clinically and may have reduced mortality. Therapy must be initiated with caution using 1/4 to 1/10 of the standard daily dose, with a very gradual increase to the standard dose, if tolerated, over several weeks.

After initial treatment of HF by β-blockers, heart rate falls, stroke volume and filling pressure are unchanged, and myocardial O_2 consumption falls. With the slower heart rate, diastolic function improves. Ventricular filling returns to a more normal pattern (increasing in early diastole) that appears less restrictive. Improved myocardial function is measurable after 6 to 12 mo, with an increase in ejection fraction, a fall in LV filling pressure, and an increase in CO. Functionally, exercise capacity appears to improve.

Carvedilol, a 3rd-generation nonselective β-blocker, is also a vasodilator with α blockade and an antioxidant. Randomized controlled trials have shown significant reduction in all-cause mortality and cardiac events in patients with mildly symptomatic CHF and ejection fraction <= 0.35. Ventricular function is significantly improved. In a patient taking stable doses of diuretics, ACE inhibitors, and digoxin, the recommended starting dose of carvedilol is 3.125 mg bid for 2 wk with cautious upward titration by doubling the dose every 2 wk to the highest level tolerated to a maximum of 25 mg bid for those weighing < 85 kg and 50 mg bid for those weighing >= 85 kg.

Vasodilators improve ventricular function by reducing systolic ventricular wall stress, aortic impedance, ventricular chamber size, and valvular regurgitation. An improved

balance between myocardial O_2 supply and demand results. Acutely ill patients with severe pulmonary congestion and deteriorating ventricular function may respond to IV nitroglycerin or nitroprusside.

Addition of hydralazine and isosorbide dinitrate to standard triple therapy of HF may improve hemodynamics and exercise tolerance and reduce mortality in refractory patients. Hydralazine is initiated at 25 mg 4 times/day and increased every 3rd day to a maximum of 300 mg/day, although most patients with refractory HF cannot tolerate dosages > 200 mg/day without developing hypotension. Isosorbide dinitrate is administered at 20 mg 3 or 4 times/day and increased to a maximum of 160 mg/day. Patients must be carefully monitored for hypotension as the dosage is increased; hospitalization may be required. Benefit may not be evident for several weeks. Except in acutely ill or refractory cases of HF, vasodilators have been replaced by ACE inhibitors, which are easier to use and usually better tolerated.

The use of **Ca blockers** in patients with reduced LV function causing HF has been disappointing. Several Ca blockers have shown a deleterious effect (nifedipine, diltiazem, verapamil) or lack of evidence of clinical or hemodynamic improvement (nisoldipine, nicardipine, felodipine).

Amlodipine is well tolerated in CHF. It significantly reduces mortality in patients with idiopathic dilated cardiomyopathy. Amlodipine (or another long-acting vasoselective Ca blocker such as felodipine) may be useful in patients with cardiomyopathy whose HF is insufficiently controlled by diuretics, ACE inhibitors, digitalis, and β-blockers. Amlodipine may also be useful in treating associated angina or hypertension.

Drug treatment of diastolic dysfunction: Patients with diastolic dysfunction may not tolerate reduced BP or plasma volume. Thus, diuretics and vasodilators are usually contraindicated. But ACE inhibitors and angiotensin II receptor blockers may reduce LV mass and stiffness and may prove to be of value. Treatment of HF in hypertrophic cardiomyopathy (see below) with a β-blocker, verapamil, or disopyramide aims to reduce cardiac contractility; thus, digoxin is also contraindicated. Successful treatment of hypertension or valve replacement for aortic stenosis will decrease LV hypertrophy and reduce ventricular stiffness. Generally, treatment of dominant systolic dysfunction will improve diastolic dysfunction. Management of patients with extensive ventricular infiltration (eg, in amyloid) remains unsatisfactory. Slowing the heart rate with a β-blocker prolongs diastole, possibly improving ventricular relaxation and allowing a more normal ventricular filling pattern.

Drug treatment of arrhythmia: Sinus tachycardia is common in HF but generally subsides with effective treatment of the HF. If tachycardia is persistent, associated causes should be sought (eg, overactive thyroid, pulmonary emboli, fever, anemia), and cautious treatment with a β-blocker may be considered. Uncontrolled atrial fibrillation may contribute importantly to LV dysfunction. Some patients have well-controlled ventricular rates at rest that become very rapid during minimal emotional or physical stress. Judicious treatment with digoxin, β-blockers, or Ca blockers (eg, verapamil, diltiazem) alone or in combination is often effective. Occasionally, dosages that control the tachycardia induce periods of asystole. Insertion of a pacemaker with maintenance on large doses of drugs that block atrioventricular conduction or complete or partial ablation of the atrioventricular node may be required. Ventricular extrasystoles are common in HF. They are generally ignored

in the absence of sustained ventricular tachycardia because most subside with successful treatment of HF.

Amiodarone, a vasodilator, has antiarrhythmic effects and direct negative inotropic action and is anti-ischemic. However, in HF, amiodarone 200 to 300 mg/day po improves LV function, possibly because its vasodilating effect overcomes its negative inotropic action. Some studies suggest improved survival in cardiomyopathy, especially hypertrophic obstructive cardiomyopathy or when of ischemic origin. Paradoxically, treatment of ventricular arrhythmia with other antiarrhythmics except β-blockers in HF has not reduced mortality.

Treatment of arrhythmia in HF may be difficult because antiarrhythmic drugs other than amiodarone and β-blockers have adverse proarrhythmic effects in the presence of LV dysfunction. If rapid atrial fibrillation does not respond to therapy with digoxin, β-blockers, or Ca blockers, nonpharmacologic treatment with permanent pacemaker insertion and complete or partial atrioventricular node ablation should be considered.

Treatment of **acute pulmonary edema** includes administration of O_2 by mask, the upright position if tolerated, morphine IV 1 to 5 mg once or twice, and IV furosemide 0.5 to 1.0 mg/kg. If hypoxia is severe (pulse oximeter) or CO_2 retention is evident (arterial blood gas), tracheal intubation and assisted ventilation may be required. Rapid evaluation of the cause of HF by history, physical examination, ECG, and, if indicated, echocardiogram should be undertaken. Specific treatment depends on etiology: a vasodilator for severe hypertension; an IV antiarrhythmic or cardioversion for supraventricular or ventricular tachycardia; and an IV Ca blocker, IV β-blocker, IV digoxin, or cardioversion to slow the ventricular rate in paroxysmal atrial fibrillation.

Acute MI is the commonest cause of acute LV failure. If BP is maintained, treatment is as above, adding sublingual nitroglycerin 0.4 mg, repeated in 5 min, followed by IV nitroglycerin 10 to 100 μg/min. A thrombolytic drug should be administered, if indicated. Because fluid status before onset of acute HF is usually normal in MI patients, diuretics are less useful and may precipitate hypotension. If BP falls or shock develops, IV dobutamine and intra-aortic balloon pump (counterpulsation) may be required. Emergency coronary angiography and evaluation for PTCA or bypass surgery may be undertaken in patients who fail to improve.

Treatment of refractory HF: Various factors may cause a failure to respond to appropriate treatment or a gradual loss of effective response after an initial favorable result. Causes include suboptimal quadruple therapy, deteriorating renal function, occult thyroid disease, anemia, treatment-induced hypotension, supervening arrhythmia (eg, atrial fibrillation with rapid ventricular response, intermittent ventricular tachycardia), alcohol consumption, and the adverse effects of concomitant drug administration (especially NSAIDs). If treatable causes are not found, additional medical therapy or referral for surgery can be considered.

Surgery: Heart transplantation is the only treatment that potentially alters the natural history of HF long-term. Currently, 1- and 3-yr survival are about 82 and 75%; however, mortality while waiting for a donor is 12 to 15%. Dynamic cardiomyoplasty has been used experimentally to boost LV function by wrapping the latissimus dorsi muscle around the heart and stimulating this skeletal muscle repetitively. Functional status has been reported

to improve in about 80% of patients. Another experimental procedure attempts to relieve wall tension by removing ventricular strips and reducing LV volume, but outcome data are limited. Several implantable ventricular assist devices are being evaluated. Ventricular assist with an external power source has been successful in supporting selected patients with refractory HF before heart transplantation. Newer devices in which the power source is inserted wholly within the body, thus reducing the major complication of infection, are also being evaluated.

End-of-life care: Death is inevitable in patients with progressive disease who are not transplant candidates and whose severe symptoms cannot be controlled. Care must focus on relief of pain and suffering (see Ch. 294).

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